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Obstructive sleep apnea and the effect of CPAP treatment on ischemia-modified albumin levels: a multi effect size meta-analysis with diagnostic test accuracy

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Abstract

Purpose A close association of oxidative stress (OS) and ischemia-modified albumin (IMA) with obstructive sleep apnea (OSA) has been reported in the literature, but the results on IMA are ambiguous. We conducted a meta-analysis to evaluate the association of IMA with OSA and the effect of continuous positive airway pressure (CPAP) therapy on IMA in patients with OSA.

Methods Relevant studies were identified by searching PubMed and other databases in addition to manual searching of cross-references. Using random-effects model, the standardized mean differences (SMDs), pooled correlation coefficients and summary of diagnostic test accuracies were obtained with 95% confidence intervals (CIs). The meta-regression, sub-group and sensitivity analyses were performed to explore heterogeneity. The presence of publication bias was tested using funnel plot analysis followed by Begg's and Egger's tests for statistical signidicance.

Results This meta-analysis finally included nine studies. When comparing with non-OSA controls, the OSA patients showed a significantly increased circulatory IMA levels (SMD = 1.15, $p = 0.0001$). And, this increase is even more pronounced in severe-OSA group as compared to mild-moderate OSA patients (SMD = 076, $p = 0.0006$). A decrease in post-CPAP treatment IMA was observed when compared with that of baseline values. Meta-analysis of correlations showed significant associations of IMA with polysomnographic parameters. The pooled diagnostic odds ratio and area under curve were 19.58 and 0.888 ($Q^* = 0.819$), respectively. There was no evidence of publication bias for the association of IMA with OSA.

Conclusion This meta-analysis suggests that OSA is associated with significantly increased IMA levels which may indicate OS, ischemia and subclinical cardiovascular risk. In the diagnostic test accuracy meta-analysis, IMA showed good accuracy for OSA detection. However, further studies are required to establish its clinical utility.

Keywords Sleep · Obstructive sleep apnea · Ischemia-modified albumin · Meta-analysis

Introduction

Obstructive sleep apnea (OSA) affects up to 5% of the general population and in a recent cohort study the prevalence of it has been found to be 23.4% in women and 49.7% in men [1, 2]. OSA has been reported to be independently associated with coronary heart diseases and increased cardiovascular morbidity and mortality [3]. OSA is characterized by periodic obstructions of the upper airways during sleep, which induces apnea and hypopnea events that are responsible for recurrent desaturation–reoxygenation sequences. Importantly, OSA patients are exposed to intermittent hypoxia (IH) due to recurrent episodes of short oxygen desaturation in the blood followed by reoxygenation. This may result in the generation of oxidative stress (OS) resulting from an imbalance between free radical formation and antioxidant defense systems. Notably,

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OS has been known to be implicated in the pathogenesis of OSA [3, 4]. The human serum albumin (HSA), a major circulatory protein that significantly contributes to the antioxidant properties by counteracting free radicals and binding to several metal ions [5]. As a result of OS, the structural and antioxidant properties of HSA have been reported to be altered in OSA patients [6].

Ischemia-modified albumin (IMA) is a modified form of HSA formed under OS conditions and it has a reduced capacity for binding of metal ions than that of normal HSA. IMA has been proposed as a novel marker of ischemia and OS useful for early detection of myocardial ischemia in cardiovascular disease [7–10]. A close association of OS in the development of OSA has been reported in the literature, but the results on IMA are ambiguous [11–19]. Continuous positive airway pressure (CPAP) therapy is known to eliminate obstructive events, prevents daytime somnolence and cardiovascular complications [20]. The CPAP treatment has been reported to normalize oxidative and antioxidative status [21].

In this study, we performed a meta-analysis to compare the circulating IMA levels between OSA patients and non-OSA controls and to assess the correlations of IMA with polysomnographic (PSG) parameters in the OSA group. We also aimed to evaluate the effect of CPAP therapy on IMA, a biomarker sensitive to ischemia and OS in OSA patients. Further, we have also performed a diagnostic test accuracy (DTA) meta-analysis for the utiity of circulatory IMA in OSA.

Material and methods

We registered the study with the International Prospective Register of Systematic Reviews (PROSPERO), having number CRD42017079496. The criteria of preferred reporting items for systematic reviews and meta-analysis (PRISMA) were followed in conduction and reporting of this systematic review and metaanalysis.

Literature search strategy

Literature serach was primarily conducted in the NCBI PubMed database using both the MESH and text word search strategies. The following search string has been developed: ("ischemia-modified albumin (IMA)"[Supplementary Concept] OR "IMA"[All Fields] OR "IMA"[All Fields]) AND ("obstructive sleep apnoea (OSA)"[All Fields] OR "sleep apnea, obstructive"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "obstructive"[All Fields]) OR "OSA"[All Fields] OR ("obstructive"[All Fields] AND "sleep"[All Fields] AND "apnea"[All Fields])). Also to retrieve articles not indexed in pubmed database; Web of science, Google scholar, Embase, Cochrane library, Springer's author mapper and science direct databases were searched for studies that reported circulating IMA level in OSA. Further, bibliographies of published articles were manually reviewed to identify additional studies. Two authors independently performed literature search and any discrepancies were resolved with discussion. Literature search was performed between 7th October 2017 (first search) and 10th January 2018 (final search) with humans set as a limit. Efforts were made to obtain data, if any, from the unpublished sources. When required, the corresponding authors of respective articles were contacted through E-mail to obtain clarification.

Study selection criteria

The studies retrieved had to meet the following criteria to be included in this meta-analysis: (1) peer-reviewed publications; (2) studies with case-control/observational design providing original data; (3) studies performed on humans with OSA diagnosis and controls; (4) studies comparing circulating IMA levels between OSA and control groups; (5) studies should have to provide IMA measurement method, units and results in means and standard deviations (SD) at baseline and/or post-CPAP treatment; (6) articles written in English. For diagnostic test accuracy meta-analysis, the included studies had to report accuracy measures of IMA in OSA. The exclusion criteria involved (1) studies reporting data in OSA patients with no control group; (2) studies where IMA results were presented in pictograms with no possibility for data extraction; (3) studies where human patients with diseases other than OSA were excluded after thouroughly reviewing full-text articles. Two authors independently performed literature search, evaluated articles for inclusion and discrepancies if any were resolved with discussion. In case of duplicate publications, only a recently published article or article with all relevant information was included.

Data extraction and quality assessment

After a thorough reading of articles satisfying inclusion criteria for this meta-analysis, the following information has been extracted: first author names, country and year of publication, number of OSA and control subjects, OSA diagnosis criteria, means and SD of age and BMI, IMA measurement method and units, CPAP treatment, correlation analysis data, ROC analysis data (Accuracy measures: sensitivity, specificity and AUC values) and other study characteristics. A quality score evaluation for studies was done according to Newcastle-Ottawa Scale (NOS) for case-control/observational studies [22]. Quality assessment of studies to maximum of eight points included three components: selection, comparability and exposure. Quality of studies included in DTA analysis was reported using "Quality assessment of diagnostic accuracy studies" (QUADAS-2) tool [23].

Statistical analysis

Meta-analyses were conducted if there were three or more studies reporting serum/plasma IMA concentrations in OSA patients in comparison to controls. Sub-group analyses were conducted on the studies evaluating serum/plasma IMA in mild-moderate and severe OSA patients. In addition, we have also compared pre and post-treatment IMA levels in OSA group.

We calculated the standardized mean difference (SMD) and its 95% confidence interval (CI) as a summary statistic for the difference of IMA level between: OSA patients and control groups; mild-moderate and severe OSA patient groups; pre- and post-treatment IMA concentrations in OSA group. Furthermore, we have also performed a meta-analysis of the correlations between IMA and polysomnographic parameters to obtain a pooled overall correlation coefficient values in the OSA group. The pooled values with 95% CIs were obtained with random-effects model. In studies where ROC data were presented, the diagnostic test accuracy meta-analysis was conducted to obtain SROC with pooled sensitivity, specificity and DOR of IMA for OSA.

The effect size for SMD and pooled correlation coefficient values were presented as a Z-score. The Z-score with a p value of < 0.05 was considered statistically significant.

The between study heterogeneity was examined by the Cochrane's Q statistic and expressed as the percentages of I^2. A p value of < 0.10 or I^2 statistic of $> 50\%$ indicated a significant heterogeneity. A random-effects model was used to compute SMD. To detect the potential source of heterogeneity, the meta-regression analysis was conducted using: study region, year of publication, sample size, age, BMI, and polysomnographic parameters. To test the robustness of this meta-analysis, a one-study leave-out sensitivity analysis was performed.

Risk of publication bias was tested with funnel plot analysis followed by Begg's and Egger's tests for statistical significance. However, to avoid the risk of bias, general search terms were chosen for a guaranteed retrieval for inclusion of articles reporting IMA levels as a secondary outcome. In case of a significant publication bias, the "trim-and-fill method" was used to correct that bias.

All comparisons were two-tailed and all analyses were conducted using the Review Manager software version 5.3 which presents SMD as Hedges g; the difference between the two means divided by the pooled standard deviation, with a correction for sample bias. The funnel plot for publication bias with Begg's and Egger's tests were performed using Comprehensive meta-analysis, version 3. The MedCalc version 16.2.0 was used for the meta-analysis of correlations. The DTA analyses were performed using Meta-Disc software, version 1.4. The heterogeneity due to threshold and non-threshold effects were assessed by Spearman correlation analysis and meta-regression, respectively. Moses linear model was used to obtain SROC curve and the pooled AUC value. The pooled sensitivity, specificity and diagnostic odds ratio (DOR) with their respective 95% CIs were obtained by using the DerSimonian Laird method.

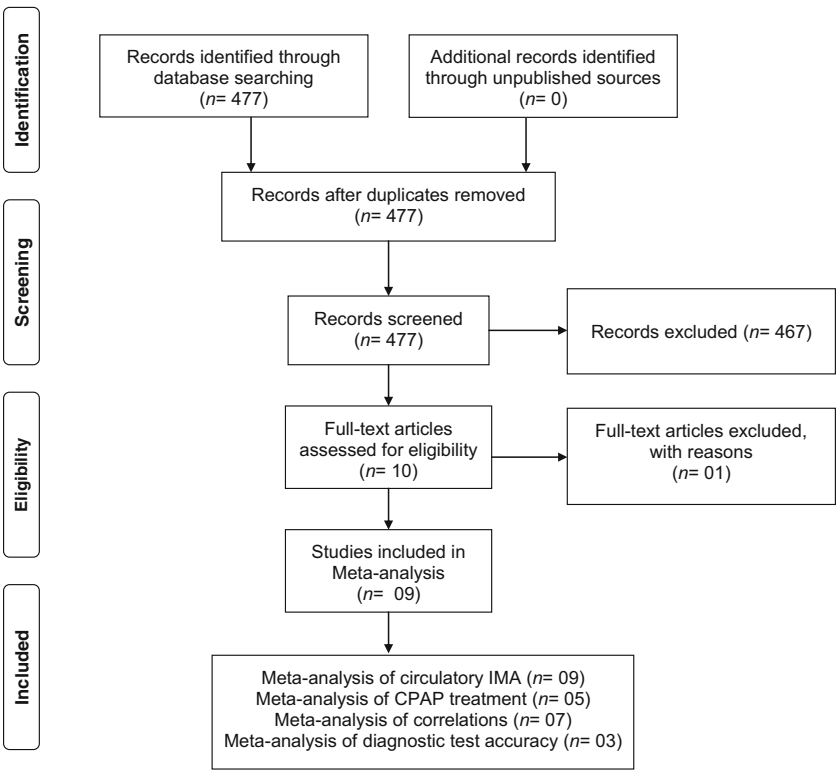

Fig. 1 The PRISMA flow diagram

Table 1 Characteristics of the included studies that evaluated circulatory IMA level in OSA patients and controls

Study, year/country [ref]	Study groups								IMA			Between OSA and CON groups		NOS
	CON			OSA										
	Age	BMI	*n*	Age	BMI	*n*	Diagnosis	Severity	Method	Sample	Units	Matching/ no-difference	Other significant differences	
Dogan et al., 2016/Turkey [11]	40.0 ± 11.7	27.3 ± 2.9	12	40.7 ± 10.7	29.2 ± 4.1	39	PSG, AASM2012	Mild-moderate, Severe	ACB-Colorimetric	Serum	U/mL	Age, BMI Alb, TG, TC, LDH, WBC	IL6, ESR,	7
Gugliucci et al., 2010/USA [12]	NA	NA	20	NA	NA	10	NA	Not clear	ACB-Versa Max from Molecular Devices	Serum	ABU	Age	NA	4
Karamanli et al., 2016/Turkey [13]	49.1 ± 10.1	30.3 ± 5.3	24	51.2 ± 9.9	32.3 ± 3.5	61	PSG	Mild-moderate, Severe	ACB-Colorimetric	Serum	ABU	Age, sex, BMI Alb, SBP, TG, LDL	AHI, ODI, TST90, SaO2	7
Ozben et al., 2014/Turkey [14]	48.6 ± 5.0	25.8 ± 3.2	25	51.0 ± 9.3	33.5 ± 5.4	59	PSG, AASM2007	Not clear	ELISA	Plasma	IU/mL	Age, sex DM	BMI,HT,SMO, TAC,TOS, AOPP, TAC	5
Oztuna et al., 2013/Turkey [15]	53.7 ± 6.5	25.8 ± 1.7	23	53.6 ± 7.1	34.8 ± 7.8	23	PSG, AASM2007	Moderate, severe	ACB-Colorimetric	Plasma	ABU	Age, sex DM, Resp Rate, DBP, NT-proBNP, Pulmonary arterial pressure	OBES, BMI, SMO, Anti-HT treat, SBP, Tei index, Epworth sleepiness score	6
Sunnetcioglu et al., 2016/Turkey [16]	35.8 ± 9.5	27.8 ± 3.9	22	46.5 ± 12.0	32.1 ± 6.3	57	PSG	Mild-moderate, Severe	ACB-Colorimetric	Serum	U/L	Sex	age, BMI, AHI, ODI, Times for SpO2 < 90%, Mean SpO2	6
Uygur et al., 2016/Turkey [17]	49.2 ± 13.1	28.9 ± 4.4	30	52.4 ± 9.7	30.3 ± 4.3	97	PSG, AASM2012	Mild, moderate, Severe	ACB-Colorimetric	Serum	ABU	Age, sex, BMI SMO, HT, DM, TST, Sleep efficiency	CRP, AHI, DSI, ESS, Mean SaO2, Stages 3-% of TST, REM,-% of TST	8
Xu et al., 2017/ China [18]	49.2 ± 13.1	28.9 ± 4.4	30	51.6 ± 9.8	30.1 ± 3.5	33	PSG	Mild-moderate, Severe	ACB-Colorimetric	Serum	ABU	Age, sex, BMI smoking, hypertension, hyperlipidemia, DM, TST, Sleep efficiency	AHI, SaO2, REM % of TST, Stage 3% of TSTMg, hsCRP	8
	40.0 ± 12.0	28.6 ± 3.1	30	40.0 ± 11.0	28.1 ± 5.5	32	PSG			Serum	U/L	Age, sex, BMI		8

Table 1 (continued)

Study, year/country [ref]	Study groups							IMA			Between OSA and CON groups		NOS
	CON		OSA										
	Age	BMI	*n*	Age	BMI	*n*	Diagnosis	Severity	Method	Sample	Units	Matching/ no-difference	Other significant differences	
Yang et al., 2013/ China [19]								Mild, moderate, Severe	ACB kit-Autoanalyzer			DM, DL, HT, AntiHT, AntiDM & Statin%, HDL	AHI, ODI, BP, TC, TG, LDL, GLU, A1C, Lowest SpO2 (%), SpO2, 90% (%TST), Butyrylcholinesterase	

OSA: obstructive sleep apnea, CON: controls, CPAP: continuous positive airway pressure treatment, AASM: American Academy of Sleep Medicine, PSG: polysomnography, IMA: ischemia-modified albumin, ACB: albumin cobalt binding, ELISA: enzyme-linked immunosorbent assay, ABU: absorbance units, BMI: body mass index, OBES: obesity, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HT: hypertension, DM: diabetes mellitus, GLU: glucose, A1C: glycated hemoglobin, SMO: smoking, TC: total cholesterol, TG: triglycerides, LDL: low-density lipoprotein, HDL: high-density lipoprotein, WBC: white blood cell, ESR: erythrocyte sedimentation rate, LDL: lactate dehydrogenase, ALB: albumin, TOS: total oxidative status, AOPP: advanced oxidation protein products, TAC: total antioxidative capacity, AHI: apnea-hypopnea index, REM: rapid eye movement, ODI: oxygen desaturation index, SaO2: arterial oxygen saturation, TST: total sleep time, ESS: Epworth sleepiness scale, TST90: total sleep time with oxyhemoglobin saturation below 90%, NA: not available, n: number of controls/OSA patients, NOS: Newcastle-Ottawa Scale

Results

Search results and study characteristics

Initially, the literature serach yielded 477 articles. Of which, 467 articles were excluded after reviewing for IMA description in OSA. After reviewing the remaining publications, one report on neurocognitive impairment and IMA data only in OSA patients was excluded [24]. Finally, a total of 9 publications comparing the circulatory IMA level between OSA patents and controls were included for conducting this meta-analysis [11–19]. Among these 9 studies, four studies distinguished IMA levels between mild-moderate and severe OSA patients [11, 16, 17, 19], and five studies evaluated the effect of CPAP treatment on IMA levels [12, 15, 17–19]. The correlations of IMA with polysomnographic evaluators have been reported; with AHI in seven studies [11, 13, 15–19], with ODI in three studies [13, 15, 17], with SaO2 in four studies [13, 15, 17, 18], and with TST90 in three studies [13, 15, 16]. Three studies reported accuracy measures and were included in the DTA meta-analysis [17–19]. The PRISMA flow diagram is shown in Fig. 1.

The characteristics and the NOS quality scores of included studies are summarized in Table 1. With the obtained score range from 4 to 8, the overall quality of studies was medium to high. In the included studies, OSA has been defined as either an AHI ≥ 5 with associated symptoms, such as sleep attacks or excessive daytime sleepiness, unsatisfying sleep, insomnia or fatigue, heavy snoring, and/or breathing pauses as witnessed by the patient's partner, or an AHI ≥ 15 regardless of the associated symptoms. The OSA severity has been categorized based on the AHI as follows: AHI between 5 and 15 as mild, AHI between 15 and 30 as moderate, and AHI > 30 as severe OSA. The controls had AHI < 5.

Circulatory IMA level in OSA compared to controls

A total of 9 studies were included in the meta-analysis of serum/plasma IMA concentrations between OSA and control groups [11–19]. Results of this meta-analysis showed that OSA patients had increased IMA level when compared with non-OSA controls. With a significant between-study heterogeneity ($I^2 = 90\%$), the random-effects model was applied to compute the pooled effect size. The pooled SMD and (95% CI) were 1.15 (0.56, 1.74). The overall effect size for SMD calculated as Z was 3.81 ($p = 0.0001$), (Fig. 2a).

IMA levels between mild-moderate and severe OSA patients

The analysis based on OSA severity revealed that, the IMA levels were significantly increased in severe OSA patients when compared with mild-moderate OSA. With a statistically non-significant between-study heterogeneity ($I^2 = 54\%$, $p =$

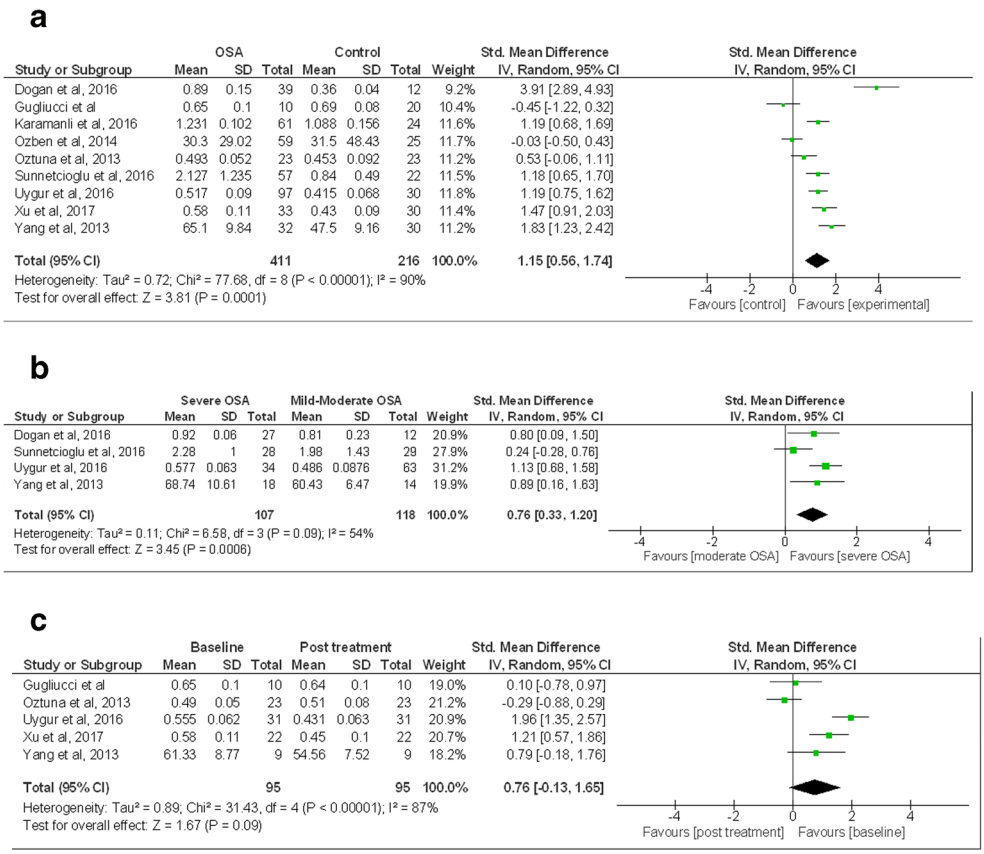

Fig. 2 The forest plot of circulatory IMA levels. **a** Between OSA and control groups. **b** Between mild-moderate and severe OSA groups. **c** Before and after CPAP treatment in OSA group

0.09), the pooled SMD and (95% CI) obtained were 0.76 (0.33, 1.20). The overall effect size for SMD calculated as Z was 3.45 ($p = 0.0006$), (Fig. 2b).

Effect of CPAP treatment

Five from the 9 included studies reported the effect of CPAP treatment on serum/plasma IMA concentrations in OSA patients [12, 15, 17–19]. The characteristics of these studies in respect of CPAP treatment are presented in Table 2. Meta-analysis based on these studies showed a decrease in post-treatment IMA level when compared with that of baseline pre-treatment values. With a significant between-study heterogeneity ($I^2 = 87\%$), the pooled SMD and (95% CI) were 0.76 (−0.13, 1.65). The overall effect size for SMD calculated as Z was 1.67 ($p = 0.09$), (Fig. 2c).

Sub-group analysis and meta-regression

As shown in Table 3, the subgroup analyses suggested that circulatory IMA concentrations in OSA patients were higher than the controls and the pooled SMD were statistically not significant in the subgroup of "plasma." This may suggest the possible source of heterogeneity among the included studies. The pooled SMDs were statistically significant in various other subgroups stratified by IMA method and units, different mean age and BMI values, and in the subgroups of studies matched for age, sex and/or BMI.

The meta-regression analysis was performed with various covariates as demonstrated in Table 4. The age (coefficient = − 0.144; SE = 0.05; $p = 0.004$) and BMI (coefficient = − 0.333; SE = 0.103; $p = 0.001$) of OSA patients yielded a statistically significant regression coefficients indicating their impact on the heterogeneity among the included studies. Because of a less number of studies, the meta-regression analysis was not performed separately on a group of studies evaluating the effect of CPAP treatment on IMA levels.

Sensitivity analysis

It was found in sensitivity analysis (Online Resource) that no single study had significantly influenced the overall pooled SMDs obtained for comparisons between OSA and controls, and mild-moderate and severe OSA groups. The combined SMDs obtained were stable and remained statistically significant after leaving-out any particular study in sensitivity analysis. Whereas, one study has significantly influenced the overall result of the effect of CPAP treatment on IMA levels in OSA. While leaving-out this study by Oztuna et al., the pooled SMD was increased from 0.76 ($Z = 1.67$, $p = 0.09$) to 1.06 ($Z = 2.68$, $p = 0.007$), with the heterogeneity decreased from 87 to 76%.

Table 2 Characteristics of the included studies that reported the effect of CPAP treatment on IMA in OSA patients

Studies [ref]	OSA patient characteristics	CPAP duration and average CPAP use	Device	CPAP titration and therapy	Effect on IMA change
Gugliucci et al., 2010 [12]	OSA sample 10 Mean-AHI (baseline) > 15	6 months	NA	NA	No significant change
Oztuna et al., 2013 [15]	OSA sample 23 m/f 22/9 Mean-AHI (baseline) 50.5	3 months. CPAP use for at least 3.5 h/night.	NA	CPAP titration was commenced at a pressure of 4 cm H_2O and gradually raised until no abnormal respiratory events were observed. The most appropriate CPAP pressure eliminating all abnormal respiratory events sleep was determined for each patient during sleep. The use of CPAP devices for at least 3.5 h per night and for 70% of nights was accepted as effective use.	No significant change
Uygur et al., 2016 [17]	OSA sample 31 Age 56.3 ± 8 m/f 22/9 BMI 31.5 ± 4.2 Mean-AHI (baseline) 26.37	3 months Average CPAP use was 6.45 ± 2.73 h/night. The mean CPAP titration pressure 7.6 ± 1.82 cm H_2O. Range from 5 to 12 cm H_2O.	(Two devices: Respironics-USA & Weinmann-Germany)	CPAP titration was started with the pressure set at 4 cm H_2O under fullnight PSG and was increased incrementally until apnoea-hypopnoea events disappeared. The lowest pressure that eliminated these events was considered the optimal pressure. A titration study was performed for at least 6 h. All participants had sufficient sleep efficiency (> 70%). Treatment compliance was measured using the built-in data stores of the CPAP device. At least 5 h/night for at least 70% of the nights/week was defined as acceptable CPAP therapy.	Significant decrease ($p < 0.001$) in serum IMA levels after 3 months of CPAP treatment.
Xu et al., 2017 [18]	OSA sample 22 BMI 31.03 ± 3.7 Mean-AHI (baseline) 19.6	3 months CPAP use was 6 h/night. The mean CPAP titration pressure 7.2 ± 1.49 cm H_2O. Range from 5 to 12 cm H_2O.	(Two devices: Respironics-USA & Weinmann-Germany)	The CPAP titration was started at an initial pressure of 4 cm H2O under overnight PSG; the pressure was then increased incrementally until apnea-hypopnea events had disappeared. Each titration study lasted at least 6 h. All participants demonstrated adequate sleep efficiency (70%).	Significant decrease ($p < 0.001$) in serum IMA levels after 3 months of CPAP treatment.
Yang et al., 2013 [19]	OSA sample 9 Age 55 ± 4 m/f 8/1 BMI 28.56 ± 1.92 Mean-AHI (baseline) 51.5	4 weeks CPAP use was 6–8 h per night. Pressure levels ranging from 7.6 to 15.6 cm H_2O.	ResMed-UK	The most optimal treatment pressure for each OSA patient was established during the first night of CPAP treatment, followed by four weeks of successive CPAP treatment during sleep. The treatment lasted 6–8 h per night with pressure levels ranging from 7.6–15.6 cm H_2O.	Significant decrease ($p = 0.019$) in serum IMA levels after 4 weeks of CPAP treatment.

OSA: obstructive sleep apnea, CPAP: continuous positive airway pressure treatment, IMA: ischemia-modified albumin, NA: not available. All of these studies in Table 2 are observational studies (not randomized controlled trials) evaluating the effect of CPAP treatment in OSA patients before and after therapy

Table 3 Results of sub-group analysis on the circulatory IMA in OSA

Circulatory IMA	No. of studies	I^2	SMD	95% CI	Overall effect (Z)	*p* value
Overall	9	90	1.15	0.56; 1.74	3.81	0.0001
Subgroup analysis						
Turkey	6	91	1.24	0.50; 1.97	3.31	0.0009
China	2	0	1.63	1.23; 2.04	7.83	< 0.0001
ACB	8	87	1.30	0.72; 1.88	4.39	< 0.0001
ELISA	1	NA	− 0.03	− 0.50; 0.43	0.14	0.89
ABU	5	80	0.83	0.28; 1.39	2.94	0.003
Other units (U/mL or U/L)	4	95	1.66	0.34; 2.98	2.46	0.01
Serum	7	88	1.42	0.78; 2.05	4.37	< 0.0001
Plasma	2	53	0.22	− 0.33; 0.76	0.78	0.44
PSG + AASM	4	94	1.32	0.14; 2.50	2.18	0.03
PSG + no AASM	5	82	1.08	0.46; 1.70	3.41	0.0006
Mean AHI < 30	2	0	1.29	0.95; 1.64	7.36	< 0.0001
AHI > 30	6	92	1.36	0.54; 2.18	3.24	0.001
Unclear AHI	1	NA	− 0.45	− 1.22; 0.32	1.14	0.25
Mean age (40–50 years)	3	91	2.23	0.93; 3.52	3.37	0.0007
Mean age > 50 years	5	83	0.86	0.32; 1.41	3.08	0.002
Mean BMI < 30	2	92	2.83	0.78; 4.87	2.71	0.007
Mean BMI > 30	6	80	0.92	0.45; 1.38	3.88	0.0001
Age-matched	8	91	1.15	0.48; 1.83	3.35	0.0008
Sex-matched	7	82	1.04	0.58; 1.50	4.42	< 0.0001
BMI-matched	5	85	1.80	1.13; 2.46	5.32	< 0.0001
Age and sex-matched	6	85	1.02	0.48; 1.56	3.69	0.0002
Age and BMI-matched	5	85	1.80	1.13; 2.46	5.32	< 0.0001
Age, sex and BMI-matched	4	15	1.37	1.09; 1.65	9.60	< 0.0001

Table 4 The meta-regression analysis of studies reporting IMA in OSA

Variables	Serum IMA			
	Coefficients	(95% CI)	SE	*p* value
Country	− 0.397	− 1.94; 1.14	0.788	0.61
Year of publication	0.237	− 0.20; 0.67	0.225	0.29
Total sample size	0.001	− 0.02; 0.02	0.014	0.92
OSA-n	0.005	− 0.02; 0.03	0.015	0.74
Control-n	− 0.067	− 0.19; 0.06	0.065	0.30
Age-Control	− 0.090	− 0.19; 0.01	0.051	0.07
BMI-Control	0.189	− 0.24; 0.62	0.221	0.39
Age-OSA	− 0.144	− 0.24; − 0.04	0.050	0.004*
BMI-OSA	− 0.333	− 0.53; − 0.13	0.103	0.001*
AHI-OSA	− 0.015	− 0.07; 0.04	0.031	0.63
TST90-OSA	− 0.004	− 0.01; 0.004	0.004	0.34
ODI-OSA	− 0.037	− 0.09; 0.02	0.029	0.19
SaO2-OSA	0.030	− 0.02; 0.08	0.028	0.27
IMA-Units	0.505	− 0.33; 1.34	0.426	0.23
Sample (Serum/Plasma)	1.189	− 0.28;2.66	0.752	0.11

*(Statistically significant), OSA: in obstructive sleep apnea group, BMI: body mass index, AHI: apnea-hypopnea index, TST90: total sleep time with oxyhemoglobin saturation below 90%, ODI: oxygen desaturation index, IMA: ischemia-modified albumin

Publication bias

There was no significant publication bias detected among the included studies (Fig. 3) according to the funnel plot asymmetry with Begg's correlation ($p = 0.46$) and Egger's regression tests ($p = 0.32$).

Meta-analysis of correlation coefficients

The results of correlation meta-analysis between IMA and PSG evaluators are demonstrated in Table 5 (Figures in Online Resource). The random-effects meta-analysis showed significant positive correlations of IMA with AHI (Pooled $r = 0.44$; $Z = 7.99$; $p < 0.001$), TST90 (Pooled $r = 0.41$; $Z = 2.96$; $p = 0.003$), ODI (Pooled $r = 0.38$; $Z = 4.38$; $p < 0.001$), and negative correlation with SaO2 (Pooled $r = -0.45$; $Z = -3.20$; $p = 0.001$).

Diagnostic test accuracy meta-analysis

Three studies reported the accuracy measures of IMA for OSA. QUADAS-2 tool was used for quality assessment of these studies (Online Resource). In all the studies, IMA

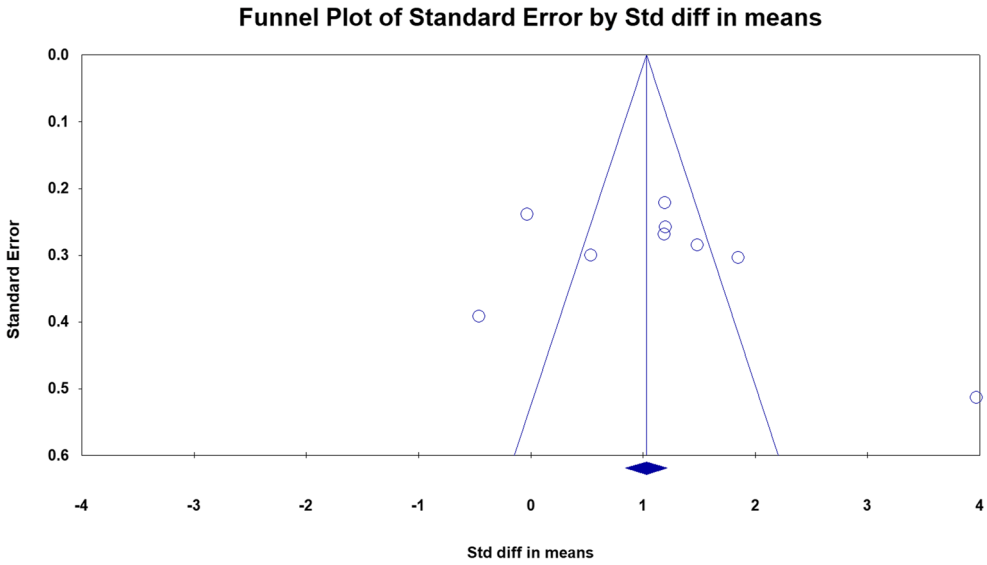

Fig. 3 The funnel plot analysis for publication bias

was measured by ACB method and the cut-off values used were not pre-specified. The results of pooled sensitivity, specificity and DOR for IMA are shown in Fig. 4. The pooled sensitivty of IMA was 0.79 (95% CI 0.72 to 0.85); whereas specificity was 0.77 (95% CI: 0.68 to 0.86). The pooled DOR of IMA was 19.58 (95% CI 9.29 to 41.24).

According to the threshold results, the *b* value of IMA was − 0.013 and *p* value was 0.98, suggesting that the SROC curve was symmetric. The obtained SROC curve for IMA, AUC and Q index are shown in Fig. 5. The pooled AUC obtained was 0.888 (Q* = 0.819). In our analysis, Spearman correlation coefficient was 0.50 with a *p* value of 0.66 indicating no heterogeneity from the threshold effect. Then we used the forest plot of DOR to explore any heterogeneity from the non-threshold effect. The result suggested there was no non-threshold effect (chi-sqaured = 1.88, *p* = 0.39). Accordingly, the meta-regression analysis conducted with several covariates produced no statistically significant regression coefficients (Online Resource).

Discussion

Findings from this meta-analysis suggest that OSA is associated with a significant increase in the circulatory IMA levels when compared with the non-OSA controls, which is indicative of increased OS status in OSA (Fig. 2a). And, this increase in IMA level was more pronounced in the "severe" OSA patients than that of "mild-moderate" OSA patients (Fig. 2b).

Our meta-analysis (Fig. 2c) to evaluate the effect of CPAP treatment on the circulatory IMA levels in OSA showed that CPAP therapy may result in the reduction of IMA levels. However, we did not notice a ststistically significant *p* value (0.09) which could be due to a less number of included studies reporting conflicting results with a significant between study heterogeneity. In most of these studies, CPAP treatment continued for 3 months, while it was only for 4 weeks in a study by Yang et al. [19]. Whereas, it is unclear in one study by Gugliucci et al. [12]. As it was revealed in sensitivity analysis, one study by Oztuna et al. [15] might have significantly influenced the overall outcome as a major contributor to the between-study heterogeneity. In their work [15], it was found

Table 5 Results of correlation meta-analysis between IMA and PSG parameters in OSA

Correlation between	Included		Heterogeneity		Meta-analysis: correlation (random effects)				
	Sample size	Studies	I^2	*p*	Pooled-r	95% CI	*Z*	*p*	Figure
IMA & AHI	354	7	14.48%	0.319	0.448	0.349; 0.537	7.993	< 0.001	Online Resource
IMA & SaO2	214	4	75.78%	0.006	− 0.457	− 0.661; − 0.189	− 3.203	0.001	
IMA & TST90	141	3	61.74%	0.073	0.411	0.147;0.621	2.963	0.003	
IMA & ODI	181	3	26.39%	0.257	0.389	0.223;0.533	4.389	< 0.001	

OSA: obstructive sleep apnea, PSG: polysomnography, IMA: ischemia-modified albumin, AHI: apnea-hypopnea index, SaO2: arterial oxygen saturation, TST90: total sleep time with oxyhemoglobin saturation below 90%, ODI: oxygen desaturation index

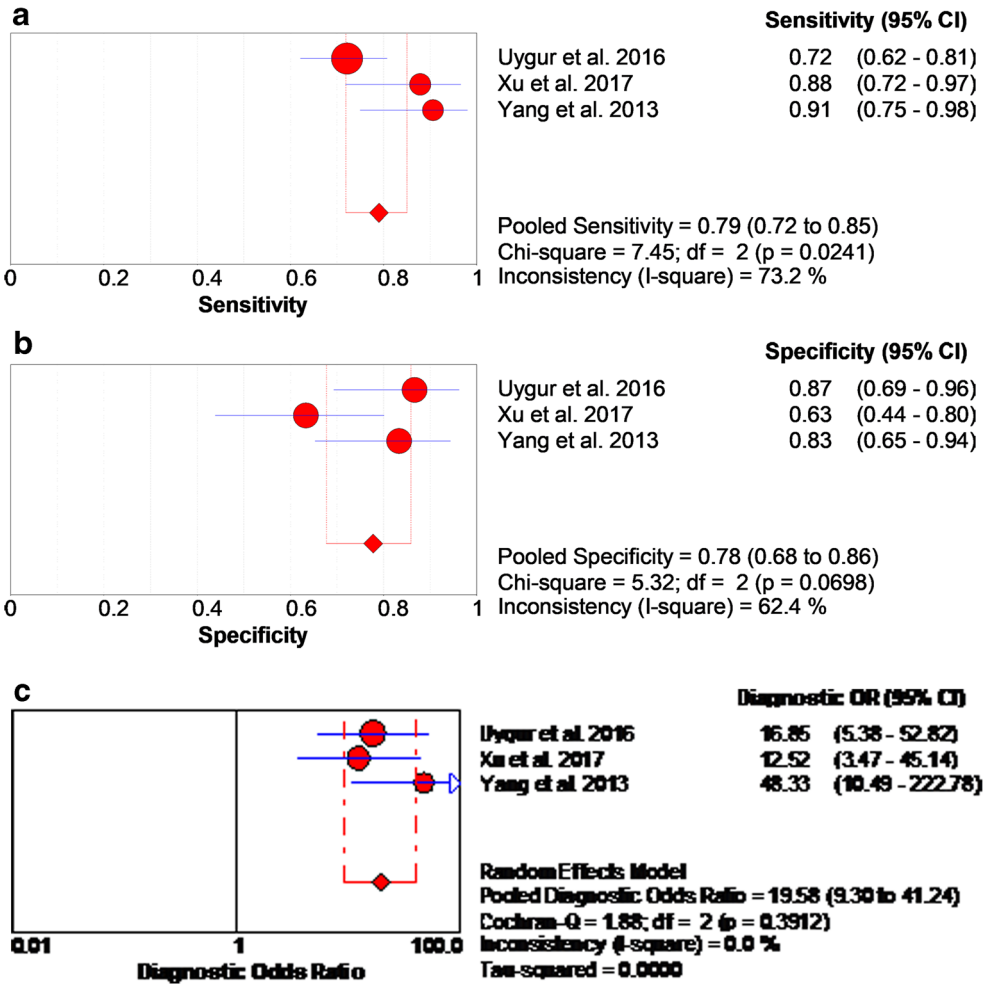

Fig. 4 The forest plots of diagnostic test accuracy meta-analysis for IMA. **a** Sensitivity. **b** Specificity. **c** DOR

that the CPAP use was 3.5 h/night which is a way lesser than other studies (6–8 h/night). Therefore, repeating this meta-analysis after leaving out the study by Oztuna et al. [15], a statistically significant *p* value (0.007) was noticed for the effect of CPAP treatment on IMA levels. Therefore, CPAP treatment is found to be effective in reversing the increased IMA indicative of elevated OS in OSA patients.

However, there are studies that did not report CPAP to reduce OS markers formed due to irreversible chemical modifications [25]. Evidence shows that repetitive episodes of hypoxia and reoxygenation in OSA patients result in the increased production of reactive oxygen species and increased OS [26]. IMA formation is known to be sensitive to these changes and can be measured by exploring its decreased meta-binding capacity due to conformational changes at the N-terminus. It is also known that IMA formation is not irreversible, with the reversal of ischemic/hypoxic and OS conditions; IMA levels may also be normalized [7]. CPAP therapy has been found to be effective in the prevention of ROS production and OS in OSA patients in addition to improving AHI, desaturation index and oxygen levels [27]. This could possibly explain the effectiveness of CPAP treatment in reversing the elevated IMA concentrations in OSA patients. All of the included studies evaluating the effect of CPAP treatment on IMA levels before and after therapy are observational studies where randomization for CPAP treatment was not done. Therefore, this limitation which may influence the quality of results warrants further investigation with randomized controlled trial design.

In OSA, each episode of airway obstruction followed by decreased arterial oxygen saturation, IH and hypoxia/reoxygenation sequences may result in increased free radical generation, OS, vascular dysfunction and inflammation. Faure et al. [6] reported structural changes and impaired antioxidant properties of serum albumin in OSA. IMA has been reported as a novel and emerging marker of ischemia, OS and inflammation [16]. In line with these evidences, our meta-analysis showed a significant increase in circulatory IMA levels in OSA patients when compared to non-OSA controls. Moreover, this increase in IMA is more evident in "severe" OSA patients as compared to that of "mild-moderate" OSA patients. This observation is further substantiated by our results of correlation meta-analysis between IMA and polysomnographic parameters. As indicated in Table 5, IMA showed a

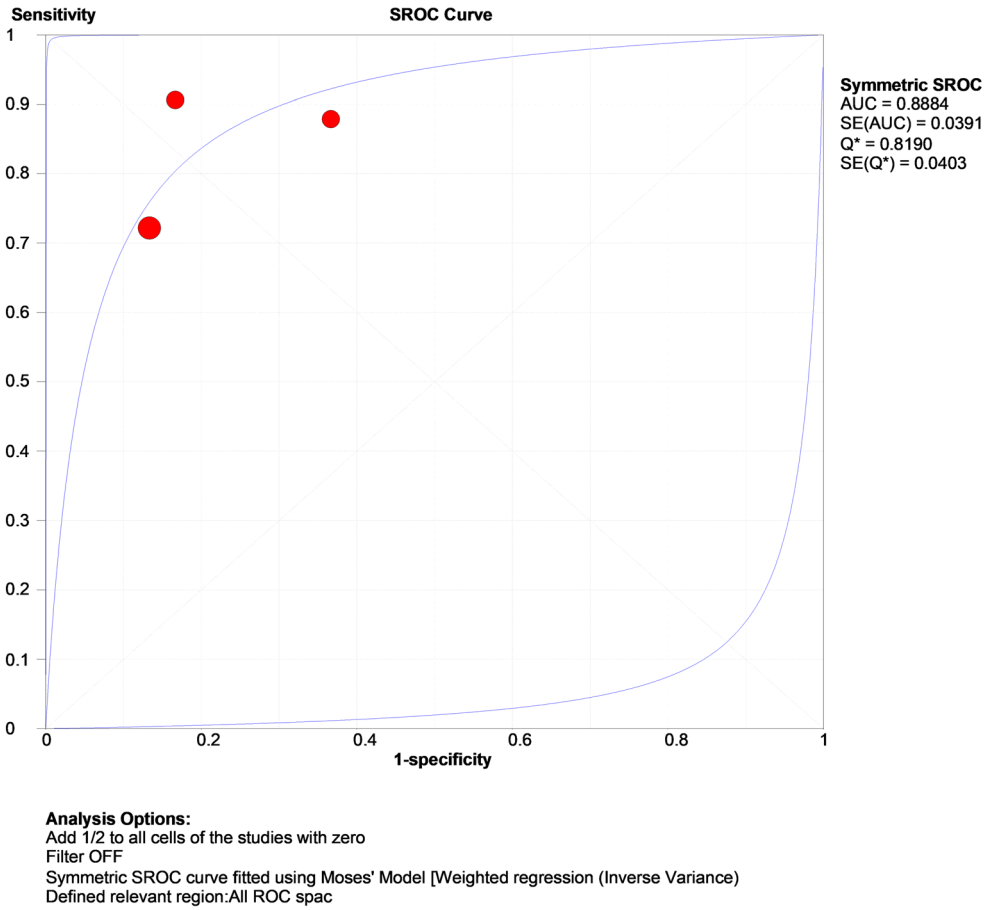

Fig. 5 SROC curve of IMA to detect OSA

significant positive correlations with AHI, TST 90 and ODI, where as there was a significant negative association of IMA with SaO2. Overall, findings of our meta-analysis primarily indicate increased circulatory IMA level suggestive of ischemia and increased OS in OSA patients, which is proportional to the severity of disease and can be reversed by CPAP treatment. As ischemia is a major concern in OSA patients, this increase in IMA may also indicate vascular dysfunction and subclinical cardiovascular risk [25–27].

Though a majority of included studies are homogenous with respect to OSA diagnosis and IMA measurement methods and matched for confounders like age, sex and BMI, there may still be some unknown source of heterogeneity. However, the presence of heterogeneity has been statistically addressed by applying the random-effects model for estimating the overall effect-size and by meta-regression and sub-group analysis. Further, a one-study leave out sensitivity analysis was conducted to test the robustness and validity of overall effect-size. The sub-group analysis (Table 3) showed that, two studies [14, 15] using plasma for IMA estimation were found to contribute significantly to the heterogeneity. Whereas, factors such as country, IMA method, AHI, Age, BMI and matching for age, sex and BMI do not significantly contribute to the heterogeneity. However, it is noteworthy that, increased body weight and obesity are important risk factors for the development and progression of OSA [15]. Age is also an important contributor in the generation of OS and our meta-regression analysis (Table 4) revealed that, age and BMI of OSA patients were a significant source of heterogeneity. The sensitivity analyses confirmed the robustness and validity of this meta-analysis as leaving-out of any single study had no significant influence on the overall effect size. Moreover, no significant publication bias was detected by the funnel plot analysis (Fig. 3) with Begg's correlation ($p = 0.46$) and Egger's regression tests ($p = 0.32$).

The currently used standard criteria for OSA diagnosis using Polysomnography (PSG) has been reported to be expensive, time-consuming and technically demanding [18, 28]. Therefore, research aimed at alternatives for OSA diagnosis would be of certain clinical importance. All the three studies included in our DTA meta-analysis enrolled mild-moderate and severe OSA patients and evaluated IMA in serum using ACB method. The pooled sensitivity and specificity of IMA were 79 and 78%, respectively. The pooled DOR and AUC of IMA were 19.5 and 0.888, repectively. Threshold effect analysis showed no heterogeneity from the threshold effect. The results of DOR also showed no heterogeneity from the non-threshold effect, which was confirmed by the results of DTA

meta-regression analysis (Online Resource). Although our results are promising and there is no significant heterogeneity, our DTA meta-analysis has several important limitations. IMA may be non-specific for OSA as it may also be produced in several other diseases involving OS [29–36]. Because of small number of included studies and relatively small sample size, further large scale studies are needed to explore IMA as a diagnostic biomarker in OSA.

It is noteworthy that hypoxia induced by OSA does not affect basal levels of the cardiac markers such as AST, troponin I, CK-MB and Pro-BNP [37]. Also, markers sensitive to ischemia could be preferred to evaluate effect of OSA on myocardial integrity. Therefore, according to our findings of this meta-analysis, IMA could possibly prove to be efficient biomarker indicative of ischemia and increased OS in OSA patients. Whereas, its diagnostic utility is limited by a less number of included studies. However, in view of previous evidence on OS as a molecular mechanism linking cardiovascular disease in OSA [26], it might be reasonable to study IMA as a possible prognostic maker for OSA complications (cardiovascular risk). Therefore, utility of IMA for OSA complications needs to be further investigated.

In summary, our meta-analysis suggests that circulatory IMA levels increase significantly in OSA patients as compared to controls. This increase in IMA was more pronounced in severe OSA patients than in mild-moderate ones and significantly associated with the PSG parameters. Further, CPAP therapy showed to decrease IMA levels in OSA patients. Overall, the increased IMA may indicate ischemia and increased OS in OSA patients. Our diagnostic test accuracy meta-analysis suggests IMA as a useful biomarker for OSA though further studies are required to establish its clinical utility in OSA.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval For this type of study, ethical approval is not required.

Informed consent For this type of study, formal consent is not required.

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